aqueous solution contained some free glycerol and some free phosphoric acid but no glycerophosphoric acid could be isolated.

Summary

1. A study has been made of the action of hot dilute alcoholic potassium hydroxide on the phosphatide A-3 from the human tubercle bacillus. When treated in this manner the phosphatide is saponified, yielding an alcoholic soap solution of the fatty acids together with small amounts of free glycerol and phosphoric acid, while an alcohol-insoluble residue remains which consists of a mixture containing a complex organic phosphoric acid and a neutral carbohydrate.

2. The organic phosphoric acid has not been studied fully but when it is boiled with dilute acid it is hydrolyzed with the formation of a reducing sugar which has not yet been identified.

3. The neutral carbohydrate, called maninositose, represents a new type of polysaccharide or a glucoside which on hydrolysis with dilute acid yields mannose and inosite.

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[Contribution from the Department of Chemistry, Yale University]

THE SYNTHESIS OF INDOLYL-BUTYRIC ACID AND SOME OF ITS DERIVATIVES

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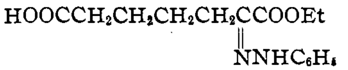
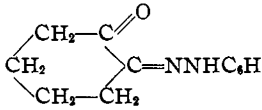
The interest which has of late centered in the metabolism of certain indole derivatives[1,2,3] has made it desirable to prepare new members, particularly some of the higher homologs, of an already known series. For example, to make available a sequence of 3-indolyl acids among which indolyl-propionic acid has heretofore been the highest known homolog, it became desirable to construct the corresponding butyric, valeric and caproic acids. At the same time, the chemical aspects of the syntheses presented several interesting features.

The recently much exploited[4] Japp and Klingemann reaction, when applied to ethyl cyclohexane-1-one-2-carboxylate, produces an excellent yield of the half ester of the phenylhydrazone of α-ketopimelic acid (I)



$$\mathrm{HOOCCH_2CH_2CH_2CH_2\underset{\overset{\|}{NNHC_6H_5}}{C}COOEt}$$

I



II

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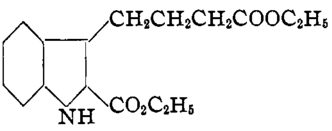
[1] Jackson, *J. Biol. Chem.*, **73**, 523 (1927); **84**, 1 (1929).

[2] Berg, Rose and Marvel, *ibid.*, **85**, 207, 219 (1929).

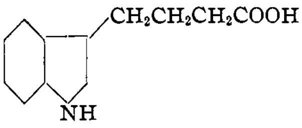
[3] Jackson, *ibid.*, **87**, XIV (1930).

[4] Manske, Perkin and Robinson, *J. Chem. Soc.*, 1 (1927); Manske and Robinson, *ibid.*, 240 (1927); and others

The alternative product, cyclohexane-1,2-dione monophenylhydrazone (II), is formed in only small amounts if at all. Esterification and indole ring closure of the ester (I) take place readily when it is heated in alcohol with sulfuric acid. The dibasic ester (III) thus obtained yields, on hydrolysis and decarboxylation, γ-3-indolyl-butyric acid (IV)



III



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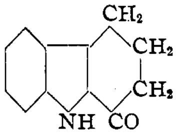
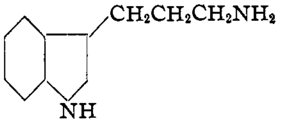


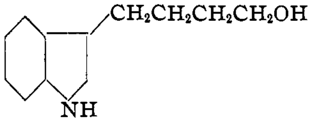
V

2-Ketotetrahydrocarbazole (V) is obtained in small amount during the decarboxylation of the dibasic acid. The temperature required for decarboxylation is presumably sufficient to induce the elimination of water—which is obviously possible and undoubtedly dependent upon the reactivity of the 2-hydrogen atom.

We have converted the indolyl-butyric acid into γ-3-indolyl-propylamine (VI) via the methyl ester, the hydrazide, the azide, the urea or the urethan and the phthalimide, and thus there is established a connection between this chain of synthetic products and a substance already known (VI)[5]



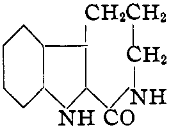
VI



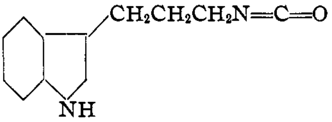
VII

Again, reduction of the ester with sodium and alcohol was found to yield δ-3-indolyl-butyl alcohol (VII); and to make the series more complete, we have, *inter alia*, prepared γ-3-indolyl-propyl alcohol by the reduction of methyl β-3-indolyl-propionate. The preparation of a lower homolog, β-3-indolyl-ethyl alcohol (the tryptophol of Ehrlich) has recently been placed on record by one of us.[6]

Lastly we attempted to synthesize the homo-3-carboline (VIII) by ring closure of the intermediary isocyanate (IX) obtained by heating the azide in an inert medium



VIII



IX

Although the similar synthesis of 2-keto-tetrahydro-3-carboline proceeds with unusual ease from the lower homologous azide,[7] our experiments in

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[5] Majima and Hoshino, *Ber.*, **58**, 2042 (1925).

[6] Jackson, *J. Biol. Chem.*, **88**, 659 (1930).

[7] Manske and Robinson, *J. Chem. Soc.*, 240 (1927).

the present case have resulted in only a small amount of the product, which appears, nevertheless, to be the desired substance. Apparently the seven-membered ring is considerably more difficult to form.

Experimental Part

Ethyl γ-(2-Carbethoxy-3-indolyl)butyrate.—It was found essential to avoid delay during this preparation as far as the isolation of the phenylhydrazone. To a mixture of 76.8 g. of aniline and 200 cc. of hydrochloric acid (sp. gr. 1.2), 56 g. of solid sodium nitrite was gradually added with constant stirring. Crushed ice was kept floating in the reaction flask during the diazotization. Meanwhile an ice-cold solution of 200 g. of potassium hydroxide in 500 cc. of water was prepared; 136 g. of ethyl cyclohexanone-carboxylate was now poured over 400–500 g. of ice; to this mixture of the ester and ice were added alternately (about ten portions of each) the solutions of the potassium hydroxide and benzenediazonium chloride such that the alkali was always present in excess. Efficient stirring was provided to prevent the formation of any localized acid regions of appreciable extent, and sufficient ice was added from time to time to keep the solution quite cold. None, or at the most only a trace, of the solid potassium salt of the cyclic ester remained at the end of the condensation. The reaction mixture was next acidified with 160 cc. of hydrochloric acid (sp. gr. 1.2) previously diluted and chilled. After standing for a short while, the half ethyl ester phenylhydrazone of α-ketopimelic acid crystallized and could then be filtered and thoroughly washed by suction. It was dried first in the air and then in a vacuum desiccator. A small quantity was recrystallized with some difficulty several times from benzene; it then consisted of an orange colored powder melting at 142–143°.[8] The yield of dried product was uniformly 200 to 204 g. The Fischer indole ring closure and attendant esterification of the free carboxyl group were conveniently effected by refluxing for two and one-half hours with 500 cc. of absolute alcohol and 55 cc. of sulfuric acid (sp. gr. 1.84). The excess alcohol was next largely distilled off under reduced pressure. The oily residue was dissolved in ether–benzene, washed with water and with aqueous sodium bicarbonate and dried over calcium chloride; after the removal of the solvent, the residue was distilled *in vacuo*. The main fraction, obtained at 235° and 7 mm., crystallized on cooling. In order to remove a small amount of oil, the distillates from three runs were united, warmed with 100 cc. of benzene to dissolve nearly all of the ester, cooled and cautiously treated with 400 cc. of petroleum ether. When crystallization was complete, the solid was filtered off and washed with petroleum ether. The yield of colorless product melting at 75–76° was 278 g. (38% of the theoretical calculated on the amount of cyclic ester employed). Recrystallization from benzene–petroleum ether yielded the ester in long needles, melting sharply at 76°.

Anal. Calcd. for $C_{17}H_{21}O_4N$: C, 67.33; H, 6.93; N, 4.62. Found: C, 67.54; H, 7.09; N, 4.75.

The methyl ester, although never obtained in as good yield, was prepared from methyl cyclohexanone-carboxylate in a strictly analogous way. The recrystallized ester consisted of colorless fine elongated plates melting at 64°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: N, 5.09. Found: N, 4.74.

During the early part of the distillation of the ethyl and methyl esters described above a colorless crystalline substance sublimed into the condenser and the top of the distillation flask. The identity of the products secured from the two distillations was suspected from their appearance and proved by a mixed melting point determination.

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[8] All recorded melting points are corrected.

Furthermore, the same substance was obtained during the preparation of the lower homologous ester from ethyl cyclopentanone-carboxylate, and a compound of analogous nature was obtained during the course of some unpublished work on the preparation of several methoxy-indole compounds.

Analytical figures and subsequent mixed melting point determination proved the substance in question to be *sym.*-diphenyl-urea (m. p. 240°).

Anal. Calcd. for $C_{13}H_{12}ON_2$: C, 73.58; H, 5.66; N, 13.21. Found: C, 73.82; H, 5.86; N, 13.18.

At present we are not prepared to submit a rational mechanism to account for the universal production of ureas under the conditions of our experiments.

γ-(2-Carboxy-3-indolyl)-butyric Acid.—The hydrolysis of the methyl and ethyl esters of this acid proceeded readily in dilute alcoholic alkali. Subsequent acidification gave quantitative yields of the acid. It was obtained from approximately 50% acetic acid in minute stout prisms melting at 193–194° with loss of carbon dioxide.

Anal. Calcd. for $C_{18}H_{13}O_4N$: N, 5.67. Found: N, 5.56.

Methyl γ-3-Indolyl-butyrate.—The dibasic acid (106 g.) was decarboxylated by heating in an oil-bath at 220° until the evolution of carbon dioxide slowed down somewhat; the decomposition of the melt was completed by elevating the temperature of the bath to 230° for fifteen minutes. The product was esterified by heating under reflux for two hours with 200 cc. of absolute methyl alcohol and 4 cc. of sulfuric acid. The ester isolated in the usual way distilled at 230° at 6 mm.; the yield was 83 g. A small amount of unchanged acid was recovered from the alkaline wash water. The ester solidified completely on cooling and when recrystallized from benzene–petroleum ether was obtained in colorless glistening plates which melted at 73–74°.

Anal. Calcd. for $C_{13}H_{15}O_2N$: C, 71.89; H, 6.91. Found: C, 72.28; H, 7.01.

γ-3-Indolyl-butyric Acid.—The crude decarboxylation residue obtained as described above is difficult to purify directly. It was found more convenient to prepare the monobasic acid by hydrolyzing the distilled methyl ester with alcoholic potash. The acid regenerated from the alkaline solution by acidification was first recrystallized from a large volume of water or from dilute alcohol but the product then tenaciously retained small quantities of water which depressed the melting point several degrees. Recrystallization from a mixture of benzene and petroleum ether gave colorless plates melting sharply at 124°.

Anal. Calcd. for $C_{12}H_{13}O_2N$: N, 6.90. Found: N, 6.77.

The hydrolysis of the monomethyl ester yielded in addition to the acid a small amount of unsaponifiable product which proved to be 2-keto-2,3,4,5-tetrahydrocarbazole the properties of which were first placed on record by Coffey.[9] Recrystallized from alcohol, it melted at 166°. The azine melted at 248°. These melting points agree with those reported by Coffey.

γ-3-Indolyl-butyric Hydrazide.—A mixture of 40 g. of 50% hydrazine hydrate, 54 g. of methyl indolyl-butyrate and 60 cc. of alcohol was placed in a flask equipped with an air-cooled reflux condenser and gradually heated in an oil-bath until the temperature rose to 130°. At the end of an hour, the condenser was removed and the temperature of the bath raised to 140–150° to effect the removal of water, alcohol and excess hydrazine. The product, which crystallized upon standing, was filtered off and washed with cold alcohol. In addition to the first yield of 35 g., a small amount was recovered by evaporating the filtrate. After one recrystallization from alcohol, the hydrazide melted sharply at 112°.

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[9] Coffey, *Rec. trav. chim.*, **42**, 531 (1923).

Anal. Calcd. for $C_{12}H_{15}ON_3$: N, 19.35. Found: N, 19.27.

Di-(γ-3-indolyl-propyl)-urea.—A cooled solution of 10 g. of the above hydrazide in 50 cc. of acetic acid was treated in rapid succession with 200 g. of ice and 4 g. of sodium nitrite dissolved in a small volume of water. The precipitated and washed azide was added in small portions to boiling water and the mixture finally heated until no more decomposition was apparent. The oily urea was washed by decantation and then freed of remaining acid and easily saponifiable matter by heating for a short time with alcoholic potash. The product precipitated by the addition of water was washed with water, dried and then heated under reflux with norite in a large volume of ethyl acetate. The clear filtered solution on evaporation yielded a pale oily residue which crystallized on cautious treatment with ether. The crystals were filtered off, washed with a mixture of ethyl acetate and ether and recrystallized from the same solvents. The yield was 2.3 g. As thus obtained the urea consists of pale yellow plates melting at 124°.

Anal. Calcd. for $C_{23}H_{26}ON_4$: N, 14.97. Found: N, 14.73.

Methyl γ-3-Indolyl-propyl-carbamate.—The azide prepared as described above was dissolved in benzene. The solution was clarified with sodium sulfate and then evaporated under reduced pressure at room temperature with frequent addition of dry benzene until all moisture had been removed. The pale yellow residue was treated with 75 cc. of absolute methyl alcohol. The solution was gently warmed until the first vigorous evolution of nitrogen subsided and then heated under reflux for twelve hours with a generous amount of norite. The clear filtrate was then repeatedly evaporated with dry benzene to remove the excess methyl alcohol. The resulting oily residue was taken up in 250 cc. of dry ether. A small amount of insoluble material was filtered off and the filtrate evaporated. Treatment with alcoholic potash removed only inappreciable impurities. Since the urethan could not be induced to crystallize, it was finally distilled *in vacuo* to give 8 g. of an almost colorless and very viscous sirup. This set to a glass on cooling and failed to crystallize in contact with various solvents. Its conversion to the phthalimide is proof of its structure.

γ-3-Indolyl-propyl-phthalimide.—For this preparation, both the urea and the urethan were found to suffice. A mixture of either substance with an equal weight of phthalic anhydride was heated in an oil-bath, finally at 230°, until effervescence ceased. The partially cooled mixture was dissolved in alcohol. The phthalimide was precipitated, while acid products were held in solution, by cautious treatment with sodium carbonate solution. The crystallized product was filtered off, thoroughly washed and recrystallized from hot alcohol, in which it is sparingly soluble. The yield of pure product consisting of pale yellowish plates and melting at 132° was nearly the theoretical amount. It is almost insoluble in ether.

Anal. Calcd. for $C_{19}H_{16}O_2N_2$: N, 9.21. Found: N, 9.03.

The mother liquors from the preparation of the urea were also suitable for making the phthalimide, which in this case was quite pure after two recrystallizations.

γ-3-Indolyl-propyl-amine.—Hydrolysis of the phthalimido compound to the amine was readily accomplished by heating with a slight excess of hydrazine in dilute alcohol. When solution was completed, the alcohol was evaporated and the aqueous solution clarified by filtration through a layer of norite. The phthalyl hydrazide obtained on acidification was filtered off. The amine was then extracted from the basified filtrate. The ethereal extract was dried over potassium hydroxide and concentrated. The residue dissolved in a small volume of acetone was carefully neutralized with dry hydrogen chloride in ether. The crystalline hydrochloride was filtered off and washed with acetone and with ether. A very good yield was secured. In agreement with data reported by Majima and Hoshino,[5] the hydrochloride melted sharply at 170°.

Anal. Calcd. for $C_{11}H_{14}N_2 \cdot HCl$: N, 13.30. Found: N, 13.06.

γ-3-Indolyl-propyl Alcohol.—To 10.2 g. of methyl β-3-indolyl-propionate dissolved in 250 cc. of absolute alcohol[10] was added 17 g. of sodium. The reaction finally was completed by heating for a short time on a steam cone. Water was added and the alcohol distilled off. The alkaline solution was extracted with ether. The residue secured by the evaporation of the ether was distilled *in vacuo* to give 6 g. of a colorless viscous oil. Further purification was effected by conversion to the picrate which on two recrystallizations from benzene was obtained in brick-red stout needles melting at 101°. The alcohol regenerated from the picrate by decomposition with alkali and distilled a second time *in vacuo* was an almost colorless oil which crystallized completely at 0° but which became liquid again at room temperature.

Anal. Calcd. for $C_{11}H_{13}ON$: N, 7.99. Found: N, 7.83.

The alcohol was further characterized by conversion to the phenylurethan formed when the alcohol was heated with a slight excess of phenyl isocyanate. The reaction mixture crystallized readily after it was washed several times with petroleum ether. The derivative was crystallized from hot benzene, in which it is only moderately soluble when cold, to give colorless plates melting at 94°.

Anal. Calcd. for $C_{18}H_{18}O_2N_2$: N, 9.52. Found: N, 9.38.

δ-3-Indolyl-butyl Alcohol.—The reduction of methyl γ-3-indolyl-butyrate (85 g.) with sodium (92 g.) and absolute alcohol (1100 cc.) in the manner described above for the lower homolog yielded 57 g. of practically colorless distillate which, on cooling and seeding with a crystal previously prepared from a specimen regenerated from the purified picrate, set to a solid mass of crystals. The material developed a slight reddish color after standing for some time.

The picrate crystallized first from dilute alcohol and then twice from benzene was obtained in ruby-colored needles melting at 102°. The alcohol liberated from the picrate by treatment with alkali was obtained as a colorless oil which slowly crystallized. A small portion plated out on porous tile melted at 32–33°.

Anal. Calcd. for $C_{12}H_{15}ON$: N, 7.40. Found: N, 7.34.

The phenylurethan recrystallized from benzene–petroleum ether melted at 88°. It is readily soluble in the ordinary organic solvents except petroleum ether.

Anal. Calcd. for $C_{19}H_{20}O_2N_2$: N, 9.11. Found: N, 9.14.

There was recovered 13 g. of indolyl-butyric acid on acidifying the alkaline solution remaining from the preparation of the corresponding alcohol. The yield of alcohol based on the ester actually used up was, therefore, 89%.

2-Keto-2,3,4,5-tetrahydro-homo-3-carboline (VIII).—The dried benzene solution of the azide prepared as described under preparation of the methylurethan (p. 5033) was gently heated on the steam-bath until evolution of nitrogen was complete. A stream of dry hydrogen chloride was passed into the solution and heating continued. A considerable amount of resin was precipitated. The clear benzene solution was evaporated to a thin sirup and the crystalline product which separated in the course of several days filtered off and washed with cold alcohol. It was recrystallized first from hot alcohol and then from acetone and was obtained in fine microcrystalline needles melting at 220°. The yield was only about 5% of the theoretical. It does not give a color with Ehrlich's reagent immediately but on prolonged boiling a cherry-red color is slowly developed. This behavior is interpreted to signify the opening of the lactam ring with subsequent decarboxylation, the latter process being analogously observed with the similar treatment of other 3-alkylated indole-2-carboxylic acids.

Anal. Calcd. for $C_{12}H_{12}ON_2$: C, 71.96; H, 6.05; N, 13.99. Found: C, 72.12; H, 6.26; N, 13.97.

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[10] Smith, *J. Chem. Soc.*, 1288 (1927).

Experiments are in progress for converting the indolyl-butyl alcohol into the *p*-toluenesulfonyl derivative with the object in view of condensing the latter with ethyl sodio-malonate[11] to obtain indolyl-caproic acid on hydrolysis and decarboxylation. We have succeeded, thus far, in securing a small amount of δ-3-indolyl-butyl malonic acid. It consists of colorless crystals melting at 177°.

Anal. Calcd. for $C_{15}H_{17}O_4N$: C, 65.43; H, 6.23; N, 5.09. Found: C, 65.47; H, 6.23; N, 5.10.

The main product by far from these reactions, however, was found to be present in a neutral fraction secured by ether extraction of an alkaline hydrolysate. The residue from this ether when distilled *in vacuo*, plated out on a porous tile and finally recrystallized from 70% alcohol yielded glistening, colorless plates which alone, or admixed with an authentic specimen of tetrahydrocarbazole prepared for comparison, melted at 117°. Further comparison of the neutral material by means of Ehrlich's color reaction failed, likewise, to disclose any difference.

Whether the ring closure is effected by the action of the acyl chloride directly on the alcohol or whether the toluene-sulfonyl ester eliminates toluene-sulfonic acid in the presence of the hot alcoholic sodium ethylate, we are not prepared to say at present. The latter course would appear to be the more likely one. In any case, however, the mechanism appears to be much the same. We are not familiar with strictly analogous examples of ring closure; the paucity of reactions of this kind is due not only to the lack of suitable orientation but also, we believe, to the absence of sufficient reactivity on the part of the hydrogen atom which must be eliminated along with the hydroxyl group as water.

Summary

1. The synthesis of indolyl-butyric acid has been effected through a procedure involving the application of the Fischer indole ring closure to the phenylhydrazone secured by subjecting ethyl cyclohexanone-carboxylate to the Japp and Klingemann reaction.

2. Along with various other derivatives, indolyl-propyl and -butyl alcohols and 2-keto-2,3,4,5-tetrahydro-homo-3-carboline were prepared. Indolyl-propylamine was synthesized via a new group of indole compounds.

3. The reactivity of the 2-hydrogen atom in the indole ring has been emphasized in light of the formation of 2-ketotetrahydrocarbazole and tetrahydrocarbazole as by-products of certain reactions employed.

4. Indolyl-butylmalonic acid has been synthesized.

NEW HAVEN, CONNECTICUT

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[11] Peacock and Tha, *J. Chem. Soc.*, 2303 (1928).